Remarks

Applicants request consideration on the merits of the above-referenced patent application.

I. Amendments to the Specification

This Preliminary Amendment makes several amendments to the specification. Pursuant to 37 C.F.R. §1.121, replacement paragraphs are provided in the previous section on pages 2-22, and a marked up version of the amendments are provided in the attached Appendix A (pages 58-85). Applicants submit that these amendments do not introduce new matter. Specifically:

In accordance with 37 CFR §1.78 and MPEP §202.01, the first paragraph in the specification has been amended to identify the patent application to which this divisional is claiming priority.

Various citations have been amended in the paragraphs bridging lines 1-14 on page 4, line 30 on page 4 to line 13 on page 5, line 28 on page 5 to line 5 on page 6, line 13 on page 521 to line 3 on page 522, lines 4-28 on page 522, and lines 4-11 on page 549. Applicants submit that these amendments correct obvious errors, and are therefore permissible under MPEP §2163.07. Applicants further submit that these amendments are supported by the cited references themselves.

The specification has been amended to replace "hydroxamate" with "hydroxamic acid" in the paragraphs bridging line 28 on page 5 to line 5 on page 6, lines 6-19 on page 6, lines 5-12 on page 7, lines 13-18 on page 7, line 19 on page 7 to line 4 on page 8, line 29 on page 35 to line 9 on page 36, lines 10-25 on page 36, lines 16-31 on page 39, lines 12-26 on page 75, lines 13-22 on page 96, and line 23 on page 407 to line 2 on page 408. In addition, the specification has been amended to indicate that the term "hydroxamic acid" includes hydroxamates in the paragraphs bridging lines 15-25 on page 1, and line 29 on page 35 to line 9 on page 36. Applicants submit that these amendments simply rephrase the specification in accordance with accepted terminology in the art, and make the language of the specification more uniform. Such amendments are proper under MPEP §2163.07.

The structures and text in the specification have been amended to replace the "Y" in the "G-A-R-E-Y", "Q-A-R-E-Y", "A-R-E-Y", "R-E-Y", and "E-Y" substituents with "Y^2". These amendments reflect the fact that the "Y" in the "G-A-R-E-Y", "Q-A-R-E-Y", "A-R-E-Y",

"R-E-Y", and "E-Y" substituents is different from the "Y" of the "X-Y-Z" ring structure between the sulfonyl and carbonyl. These amendments are consistent with the claim amendments, and are supported by Applicants' specification at, for example, claims 1, 6, 17, 25, 42, and 50 (as originally filed); line 24 on page 16 to line 4 on page 18; and line 27 on page 21 to line 10 on page 24. Specifically, this text defines Y differently depending on whether it is a part of the G-A-R-E-Y, Q-A-R-E-Y, A-R-E-Y, R-E-Y, or E-Y substituent or part of the X-Y-Z ring structure between the carbonyl and sulfonyl.

The chemical structures in Schemes B and C on pages 104 and 106 have been amended to include two bonds between the sulfur and oxygen(s). This amendment corrects an obvious error. It also is supported by Applicants' specification at, for example, page 99, line 29 to page 100, line 8; page 103, lines 11-16; and page 104, lines 5-9. Specifically, this text points out the fact that the schemes illustrate that the sulfur in the structures may be part of a thio, sulfoxide (which is -S(=O)-), or sulfone (which is $-S(=O)_2-$).

Other amendments simply rephrase the specification, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

II. Amendments to the Claims

This Amendment A cancels claims 1-66, and adds new claims 67-114. Thus, claims 67-114 are pending. These claims are shown in the previous section on pages 23-49. Applicants submit that these claims do not encompass new matter. Specifically:

As discussed in more detail below, the substituent definitions in the claims have been restricted in accordance with Applicants' election of Group IV for examination in this divisional application. Specifically, the Q definition has been restricted to non-piperazinyl rings; R^{20} has been restricted to $-NH-O-R^{14}$; and the X, Y, and Z definitions have been restricted to exclude O and NR^6 from Part (a) of the definitions.

Claim 67 is supported generally by Applicants' specification at, for example, claim 25 (as originally filed), Formula B-1 on page 64, and Formula XI on page 67. The "R" definition, however, has been revised to replace "heterocycloalkyl" with "heterocyclo". This amendment is consistent with the language at, for example, page 90, lines 26-33 of Applicants' specification. It

also is supported in Applicants' specification by, for example, the sulfonyl substituent shown in Example 807.

Claims 68 and 87 are supported generally by Applicants' specification at, for example, claim 1 (as originally filed (line 7 on page 558)), and lines 5-12 on page 31.

Claims 69, 84, and 90 are supported generally by Applicants' specification at, for example, claims 1, 6, 25, 42, and 50 (as originally filed (lines 8-16 on page 563, line 27 on page 572 to line 5 on page 573, lines 6-16 on page 591, line 25 on page 59 to line 2 on page 599, and lines 18-23 on page 605), and line 26 on page 27 to line 5 on page 28.

Claims 70 and 92 are supported by Applicants' specification at, for example, claim 29 (as originally filed).

Claims 71 and 93 are supported by Applicants' specification at, for example, claim 30 (as originally filed).

Claim 72 is supported by Applicants' specification at, for example, claim 26 (as originally filed).

Claims 73 and 81 are supported by Applicants' specification at, for example, claim 28 (as originally filed).

Claim 74 is supported by Applicants' specification at, for example, Formula B-1A on page 64.

Claims 75 and 95 are supported by Applicants' specification at, for example, claim 33 (as originally filed).

Claims 76 and 96 are supported by Applicants' specification at, for example, claim 34 (as originally filed).

Claims 77 and 97 are supported by Applicants' specification at, for example, claim 35 (as originally filed).

Claim 78 is supported by Applicants' specification at, for example, Formula B-1 on page 64; and line 20 on page 63 to line 8 on page 64.

Claim 79 is supported by Applicants' specification at, for example, claim 42 (as originally filed), Formula B-1A on page 64, and line 20 on page 63 to line 8 on page 64.

Claim 80 is supported by Applicants' specification at, for example, the R definition in claims 1, 25, and 42 (as originally filed).

Claims 82 and 101 are supported by Applicants' specification at, for example, claims 18, 43, and 56 (as originally filed).

Claim 83 is supported by Applicants' specification at, for example, claim 3 (as originally filed), and Formula B-2 on page 65.

Claim 85 is supported by Applicants' specification at, for example, Formula XI-1 on page 67, and claim 42 (as originally filed).

Claim 86 is supported by Applicants' specification at, for example, 6, 17, and 50 (as originally filed). The "Y^2" definition, however, has been revised in the following manner:

A. The Y^2 definition does not recite hydrogen as one of the possible Y^2 substituents.

B. The Y^2 definition expressly recites heterocyclo (optionally substituted with the recited optional substituents) as one of the possible Y^2 substituents. This amendment is supported in Applicants' specification by, for example, the sulfonyl substituents shown in Examples 3, 6-34, 36-44, 46, 47, 49, 50, 54, 55, 162, 233, 234, 238-241, 246, 274-315, 456, 458, 686, 807, and 873.

C. The Y^2 definition expressly recites alkyl as one of the optional substituents of the aryl, heteroaryl, aralkyl, heterocyclo, and heterocycloalkyl. This amendment is supported in Applicants' specification by, for example, the sulfonyl substituents shown in Examples 3, 19, 34, 46, 47, 54, 55, 84, 162, 233, 234, 238-241, 274-315, 370, 371, 373, 383, 456, 458, 490, 494, 535, 536, 542, 589, 652, 653, 671, 674, 684, 730, 732-734, 736, 737, 788, 789, 807, 822, 823, 834, 858, 860, 867, 869, 878, 888, 905, 906, 909, and 922. It also is supported by Applicants' specification at, for example, page 90, lines 35-37, page 92, lines 1-8.

Claim 88 is supported by Applicants' specification at, for example, claim 22 (as originally filed), and Formula VIC-2 on page 65.

Claim 89 is supported by Applicants' specification at, for example, claims 24, 50, and 55 (as originally filed), and Formula IX-2 on page 66.

Claim 91 is supported by Applicants' specification at, for example, the "Y" definitions in claims 6, 17, and 50 (as originally filed (line 20 on page 573 to line 4 on page 574, line 22 on page 582 to line 7 on page 583, and lines 8-24 on page 606)).

Claim 94 is supported by Applicants' specification at, for example, Formula B-3A on page 65.

Claim 98 is supported by Applicants' specification at, for example, Formula VIC-1 on page 65; and claim 21 (as originally filed).

Claim 99 is supported by Applicants' specification at, for example, claims 23, 50, and 54 (as originally filed), and Formula IX-1 on page 66.

Claim 100 is supported by Applicants' specification at, for example, the "Y" definition in claims 6, 17, and 50 (as originally filed (line 20 on page 573 to line 4 on page 574, line 22 on page 582 to line 7 on page 583, and line 8-24 on page 606).

Claim 102 is supported by Applicants' specification at, for example, Example 153 on pages 364-365.

Method-of-treatment claims 103 and 108 are supported by Applicants' specification at, for example, claims 1, 6, and 17 (as originally filed), lines 5-12 on page 31, line 13 on page 34 to line 13 on page 35, lines 17-20 on page 35, and line 5 on page 302 to line 21 on page 307.

Method-of-treatment claim 104 is supported by Applicants' specification at, for example, claims 3, 27, 46, and 47 (as originally filed).

Method-of-treatment claims 105, 106, 109, and 110 are supported by Applicants' specification at, for example, lines 21-27 on page 34.

Method-of-treatment claims 107 and 111 are supported by Applicants' specification at, for example, claims 5 and 16 (as originally filed); and lines 12-21 on page 304.

Composition claims 112 and 114 are supported by Applicants' specification at, for example, claims 62, 63, and 65 (as originally filed), lines 5-12 on page 31, line 13 on page 34 to line 13 on page 35, lines 21-23 on page 35, and line 36 on page 304 to line 21 on page 307.

Composition claim 113 is supported by Applicants' specification at, for example, claims 3, 27, 46, 47, and 64 (as originally filed).

To the extent claims 67-114 are supported by one or more of the originally-filed claims, differences may exist due to the removal redundancies or unnecessary terms, correction of grammatical or obvious errors, and/or rephrasing. Such changes are permissible under MPEP §2163.07, and are not intended to affect the scope of the claims. For example:

A. The “Y” in the "A-R-E-Y", "R-E-Y", and "E-Y" substituents has been replaced

with "Y^2" to reflect the fact that it is different from the "Y" of the X-Y-Z ring structure between the sulfonyl and carbonyl. This amendment is supported by Applicants' specification at, for example, claims 1, 6, 17, 25, 42, and 50 (as originally filed); line 24 on page 16 to line 4 on page 18; and line 27 on page 21 to line 10 on page 24. Specifically, that text provides two definitions for "Y": one for the Y in the ring structure, and one for the Y of the A-R-E-Y, R-E-Y, or E-Y substituent.

B. The term "hydrido" has been replaced with "hydrogen" to make the claim language more uniform.

C. The abbreviation "ar" has been replaced with "aryl" to make the claim language more uniform. This amendment is supported by Applicants' specification at, for example, page 94, line 14 to page 95, line 22.

D. The term "heterocyclic" has been replaced with "heterocyclo" to make the claim language more uniform. This amendment is supported by Applicants' specification at, for example, page 90, line 26.

E. The term "pharmaceutically acceptable cation" has been removed from the R^{14} definitions. This removes a redundancy. More specifically, the claims already refer to both compounds and their salts. Including the presence of a cation in the R^{14} definition is therefore redundant.

F. The term "cycloalkoxy" has been replaced with "cycloalkyloxy" in the R definitions. This amendment is consistent with the language in Applicants' specification at, for example, page 90, lines 11-25. This amendment also is supported (by analogy) by the discussion relating to "phenoxy" on page 94, lines 24-27.

G. The "C_5-C_6-" modifier for heterocyclo and heteroaryl R^6 and $R^{6'}$ definitions has been replaced with "5- to 6-membered". This amendment makes the claim language clearer, and is supported by Applicants' specification at, for example, page 91, lines 14-15 and 19-21. Similarly, the "C_3-C_8-" modifier for heterocycloalkyl has been replaced with "3- to 8-membered".

H. The phrase "the sulfoxide or sulfone of any said thio substituents" in the R^8, R^9,

R^{10}, R^{11}, R^{12}, and $R^{12'}$ definitions has been replaced with the specific substituents to which the phrase refers.

I. The term "heterocycloalkyl-C_1-C_6-alkyl" in the R^8, R^9, R^{10}, R^{11}, R^{12}, and $R^{12'}$ definitions has been replaced with "heterocyclo-C_1-C_6-alkyl". This amendment is consistent with the language at, for example, page 90, lines 26-33 of Applicants' specification.

Applicants reserve the right to pursue any canceled and/or unclaimed subject matter in a divisional and/or continuation application(s).

III. Scope of Pending Claims

In the parent application (U.S. Appl. No. 09/570,731), examination was restricted to subject matter falling within Group II outlined in the May 31, 2001 restriction requirement of that application. Group II encompasses compounds and salts where Z is -N(R^6)-; m+n+p is 2; and Q is piperidinyl. It also encompasses methods-of-treatment using such compounds and salts, and compositions comprising such compounds and salts.

In the instant divisional application, Applicants elect subject matter falling within **Group IV** of the May 31, 2001 restriction requirement. This group encompasses compounds and salts wherein R^{20} is -NH-O-R^{14}, except for any such compounds or salts where: (1) Q is piperazinyl and m+n+p is 2, (2) Z is NR^6, Q is piperidinyl, and m+n+p is 2, or (3) Z is NR^6, Q is piperidinyl, and m+n+p is 2. This group also encompasses methods of treatment using such compounds and salts, and compositions comprising such compounds and salts.

Applicants further elect the compound recited in **claim 102** (*i.e.*, Example 153 on page 364-365) as the starting point for examination of the compound claims, and **osteoarthritis** as the starting point for examination of the method-of-treatment claims.

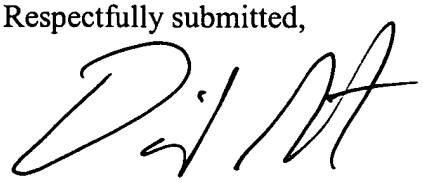
* * * * * * * * *

Applicants submit that the pending claims are in condition for allowance. Applicants have enclosed a check to cover the filing fee for this application. Applicants do not believe that they owe any additional fee in connection with this filing. If, however, Applicants do owe any such additional fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit

Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

The Examiner is requested to call the undersigned if any questions arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,



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Appendix A
Marked-Up Version of Amendments to Specification

The paragraph bridging lines 7-12 on page 1 has been amended in the following manner:

This **patent is a divisional of U.S. Application Serial No. 09/570,731 (filed on May 12, 2000), which, in turn,** is a continuation-in-part of **U.S. Application** ~~application~~ Serial Nos. 09/311,837 (filed on May 14, 1999) **and** ~~that was a continuation-in-part of application Serial No.~~ 09/256,948 (filed on February 24, 1999). ~~, that was~~ **U.S. Application Serial No. 09/311,837 claims priority as** a continuation-in-part of ~~application~~ **U.S. Application** Serial Nos. **09/256,948, 09/191,129** ~~09/74497~~ (filed on November 13, 1998), **and 09/186,410 (filed on November 5, 1998); and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007 (filed on November 14, 1997), 60/095,347 (filed on August 4, 1998), 60/095,501 (filed on August 6, 1998), and 60/101,080 (filed on September 18, 1998). U.S. Application Serial No. 09/256,948 claims priority as a continuation-in-part of U.S. Application Serial Nos. 09/191,129 and 09/186,410; and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. U.S. Application Serial No. 09/191,129 claims priority as a continuation-in-part of U.S. Application Serial No. 09/186,410; and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. And U.S. Application Serial No. 09/186,410 claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. The entire text of each of the above-referenced patent applications are incorporated by referenced into this patent**.

The paragraph bridging lines 15-25 on page 1 has been amended in the following manner:

This invention is directed to proteinase (protease) inhibitors, and more particularly to the use of aromatic sulfone hydroxamic acid compounds **(including hydroxamates)** that, *inter alia*, are selective inhibitors of matrix metalloproteinases in a process for treating conditions associated with pathological matrix metalloproteinase activity, the selective inhibitors

themselves, compositions of proteinase inhibitors, intermediates for the syntheses of proteinase inhibitors, and processes for the preparation of proteinase inhibitors.

The paragraph bridging lines 1-14 on page 4 has been amended in the following manner:

TNF-α convertase is a metalloprotease involved in the formation of soluble TNF-α. Inhibition of TNF-α convertase (TACE) inhibits production of active TNF-α. Compounds that inhibit both MMPs activity and TNF-α production have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature*, **370** [[376]], 555-557 (1994), McGeehan et al., *Nature*, **370** [[376]], 558-561 (1994)). There remains a need for effective MMP inhibitors. There also remains a need for effective TNF-α convertase inhibiting agents.

The paragraph bridging line 30 on page 4 to line 13 on page 5 has been amended in the following manner:

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin, gelatinase A or B, or collagenase III appear to be the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation of inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chrondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, **97(3)**:761-768 (1996) and Reboul et al., *J. Clin. Invest.*, **97(9)**:2011-2019 (1996).

The paragraph bridging line 28 on page 5 to line 5 on page 6 has been amended in the following manner:

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, ~~WO95/12389~~ **WO 95/13289**, WO 96/11209 and U.S. 4,595,700. **Hydroxamic acid** ~~Hydroxamate~~ group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose **hydroxamic acids** ~~hydroxamates~~ that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem., 29:*271-334(1992) and those of Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997) and Denis et al., *Invest. New Drugs, 15* **[[*(3)*]]**: 175-185 (1997).

The paragraph bridging lines 6-19 on page 6 has been amended in the following manner:

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic **hydroxamic acid** ~~hydroxamate~~ known as batimastat is reported to exhibit IC_{50} values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic **hydroxamic acid** ~~hydroxamate~~ was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC_{50} value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997).

The paragraph bridging lines 5-12 on page 7 has been amended in the following manner:

International application WO 98/38163, published on September 3, 1998 disclose a large group of **hydroxamic acid** ~~hydroxamate~~ inhibitors of MMPs and TACE. The compounds of WO 98/38163 contain one or two substituents adjacent to the **hydroxamic acid** ~~hydroxamate~~

functionality and a substituent that can be an aromatic sulfonyl group adjacent to those one or two substituents.

The paragraph bridging lines 13-18 on page 7 has been amended in the following manner:

International application WO 98/37877, published on September 3, 1998 discloses compounds that contain a 5- to 7-membered heterocyclic ring adjacent to the **hydroxamic acid** ~~**hydroxamate**~~ functionality and can contain an aromatic sulfonyl group adjacent to the heterocyclic ring.

The paragraph bridging line 19 on page 7 to line 4 on page 8 has been amended in the following manner:

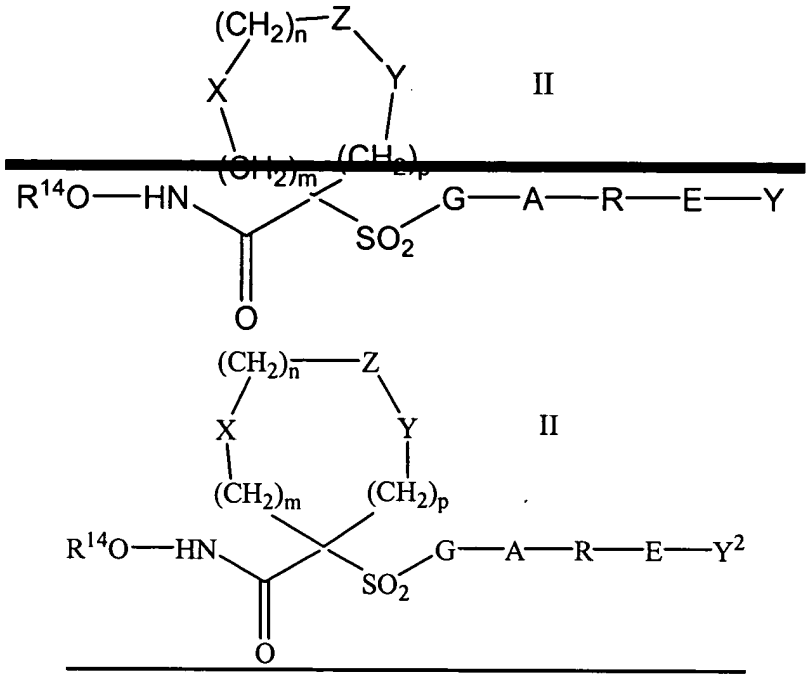
Although many of the known MMP inhibitors such as batimastat, marimastat and the **hydroxamic acids** ~~**hydroxamates**~~ of WO 98/37877 and WO 98/38163 exhibit a broad spectrum of activity against MMPs, those compounds are not particularly selective in their inhibitory activity. This lack of selectivity may be the cause of the musculoskeletal pain and stiffness observed with their use. In addition, it can be therapeutically advantageous to utilize a medicament that is selective in its activity as compared to a generally active material so that treatment can be more closely tailored to the pathological condition presented by the host mammal. The disclosure that follows describes a process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that utilizes a compound that selectively inhibits one or more MMPs, while exhibiting less activity against at least MMP-1.

The paragraph bridging line 30 on page 12 to line 2 on page 13 has been amended in the following manner:

Preferably, the R^3 substituent is Ph-Q-A-R-E-Y^2 wherein Ph is phenyl substituted at the 4-position relative to the depicted SO_2 group, and -Q-A-R-E-Y^2 is a substituent in which Q is a 5- to 7-membered heterocyclic ring containing one or two nitrogen atoms, one of which is bonded the depicted phenyl group, and whose remaining members are defined hereinafter for the

substituent G-A-R-E-Y^2.

Formula II at line 1 on page 16 has been amended in the following manner:



The paragraph bridging line 27 on page 21 to line 4 on page 22 has been amended in the following manner:

G-A-R-E-Y^2 is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y^2 preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

The paragraph bridging lines 24-25 on page 23 has been amended in the following manner:

(9) E is absent and R is bonded directly to Y^2; and

The paragraph bridging line 26 on page 23 to line 10 on page 24 has been amended in the following manner:

the moiety Y^2 is absent or is selected from the group consisting of a hydrido, alkyl,

alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl, aralkyl, or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, trifluoroalkyl, trifluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

The paragraph bridging lines 20-23 on page 24 has been amended in the following manner:

m, n, p, X, Z, Y and R^{14} are as defined above for formula II, and the R^3 radical that is defined below is a sub-set of the previously discussed G-A-R-E-Y^2 substituents.

The paragraph bridging lines 3-6 on page 26 has been amended in the following manner:

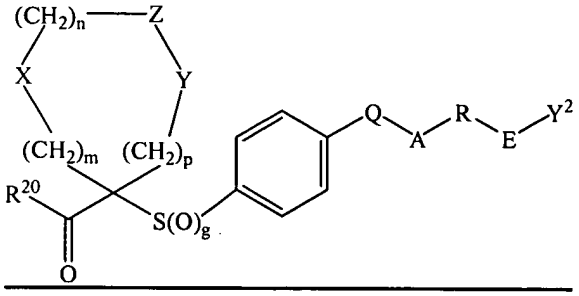
wherein R^3 is as defined above for formula I, more preferably as defined for formula II (wherein this R^3 group is the G-A-R-E-Y^2 substituent), and more preferably still as defined for formula III, and

The paragraph bridging line 15 on page 27 to line 10 on page 28 has been amended in the following manner:

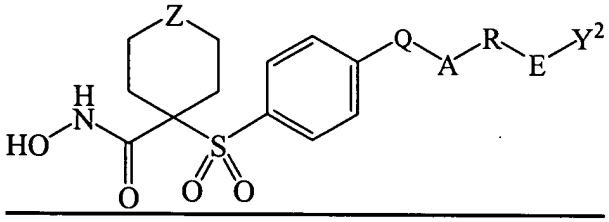
Further compounds of formula A are also particularly preferred. One group of these compounds corresponds in structure to formula B (including formulas B, B-A, B-1, B-1A, B-2, B-2A, B-3 and B-3A), formula VIC, and more still particularly to formula VIC-1 and formula VIC-2, and formula VIII, below. In those formulas, ring structure Q is a substituent of the depicted phenyl ring and can itself be substituted. Substituent Q including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 7-members, preferably 6-members, and can contain zero or one additional nitrogen atom. The substituents of Q such as A-R-E-Y^2, R-E-Y^2 and E-Y^2 are as defined before, and such a substituent is bonded at the 4-position relative to that depicted

nitrogen atom when Q is a 6- or 7-membered ring and at the 3- or 4- position relative to that depicted nitrogen when Q is a 5-membered ring. The remaining members of such a ~~Q-beraing~~ **Q-bearing** substituent (e.g., A-R-E-Y^2) are defined herein for the substituent G-A-R-E-Y^2. In addition, R^{20}, X, Y, Z, m, n, and p of the ring system and g are as before described, with Z preferably being O or NR^6.

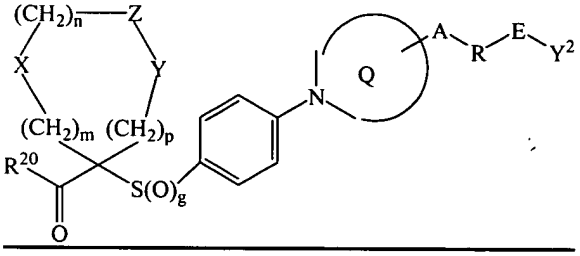
The structures from line 11 on page 28 to line 2 on page 30 have been amended in the following manner:



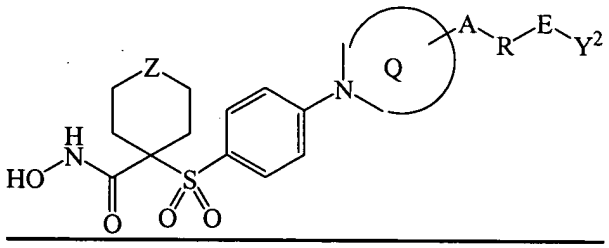
B



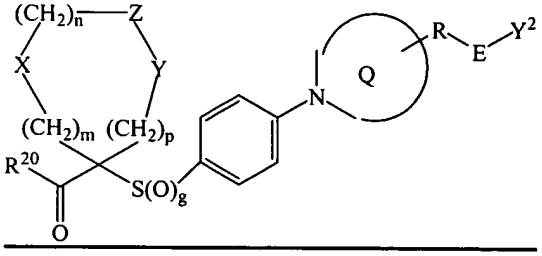
B-A



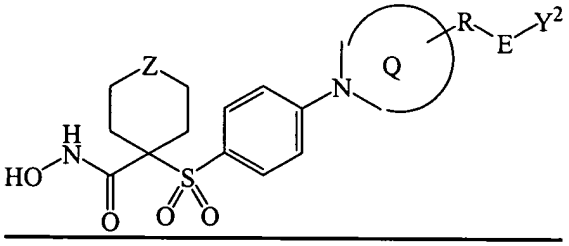
B-1



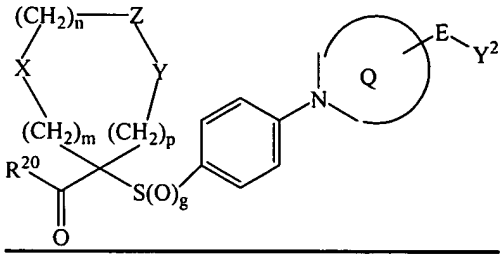
B-1A



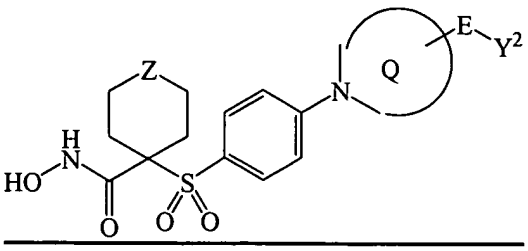
B-2



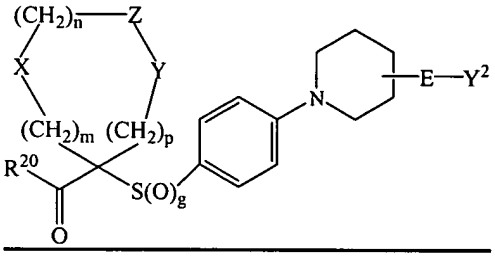
B-2A



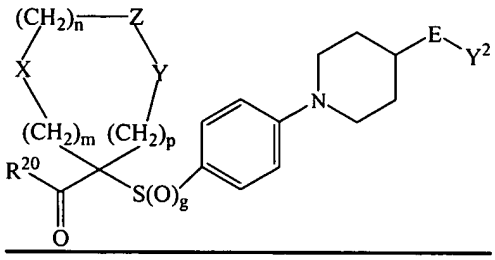
B-3



B-3A



VIC



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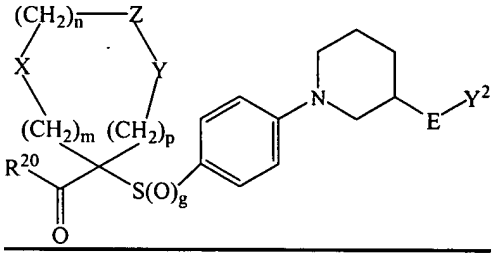
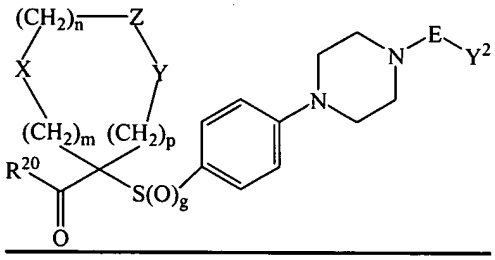
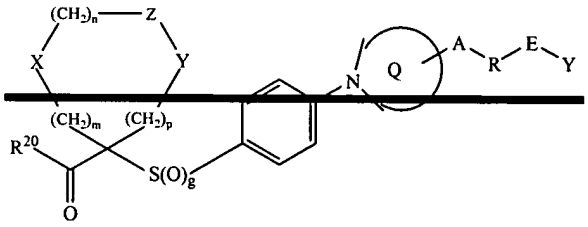


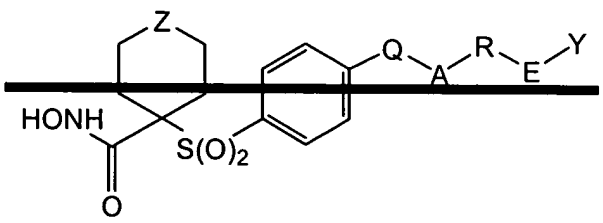
VIC-2



VIII



~~**B**~~



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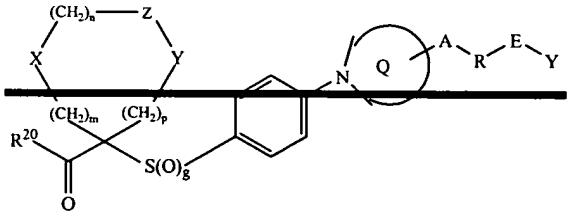

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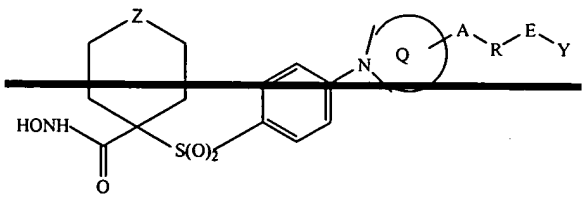

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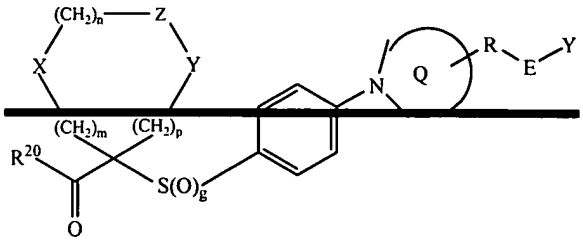

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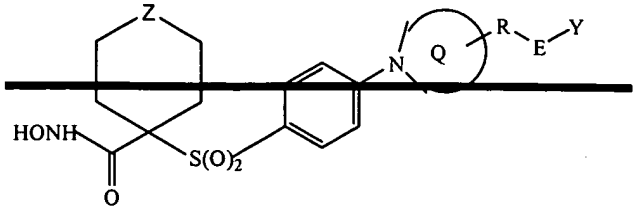

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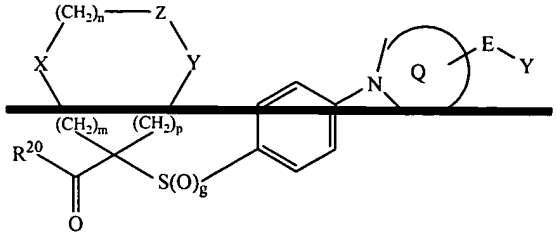

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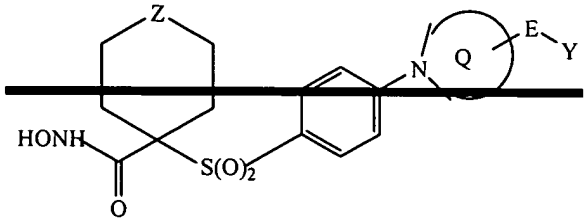
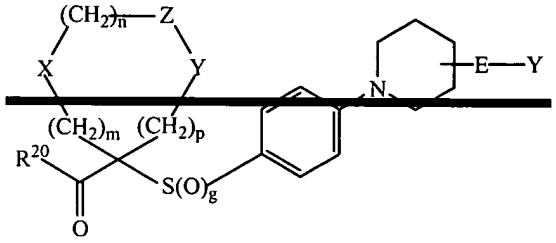
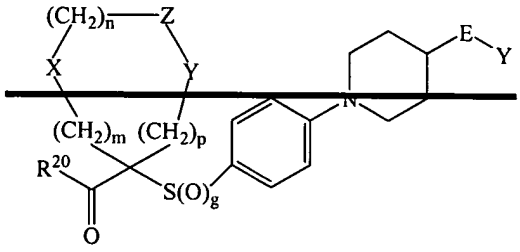


~~B-3A~~



~~VIC~~



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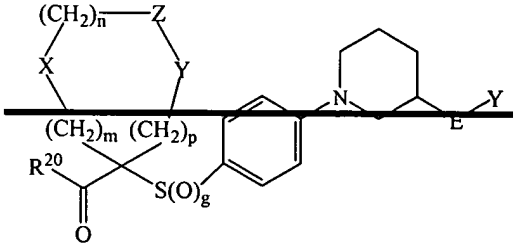
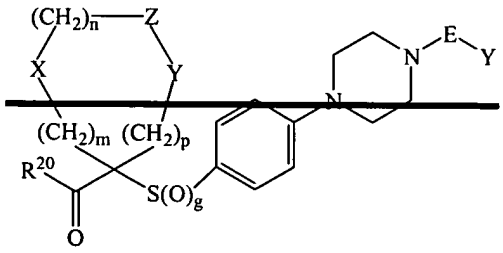


~~VIC-2~~



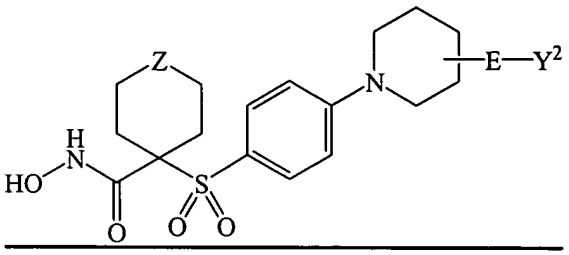
~~VIII~~

The paragraph bridging lines 3-17 on page 30 has been amended in the following manner:

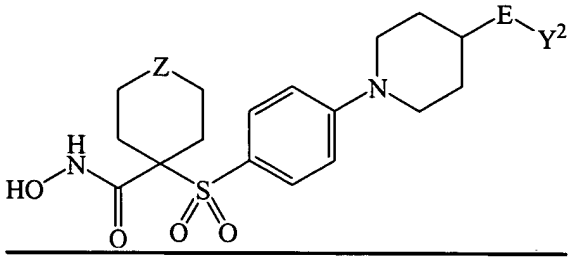
The compounds of formulas IX, IX-1, IX-2, X, XI, XI-1, XI-2 and XII, below, are more particularly preferred among the compounds of formula VIC, formula VIC-1, formula VIC-2, and formula VIII. In those latter formulas, Z is as before described, with Z preferably being O or NR^6, and substituent Q is a 6-membered ring, as is shown. The A moiety of the Q ring substituent -A-R-E-Y^2 (e.g. of formula B or B-1) is preferably absent in some embodiments, as

in the compounds of formulas XI through XII, whereas both moieties A and R of that substituent group are absent in compounds of formulas IX through X. The moieties A, R, E and $Y^{\underline{2}}$ of the substituent group -A-R-E-$Y^{\underline{2}}$ are defined for the substituent group -G-A-R-E-$Y^{\underline{2}}$.

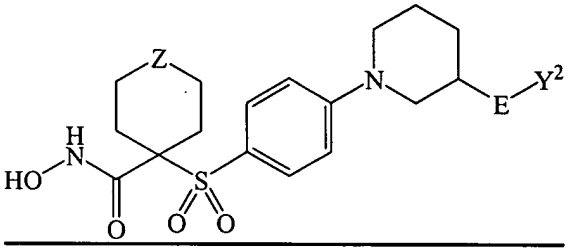
The structures from line 18 on page 30 to line 4 on page 31 have been amended in the following manner:



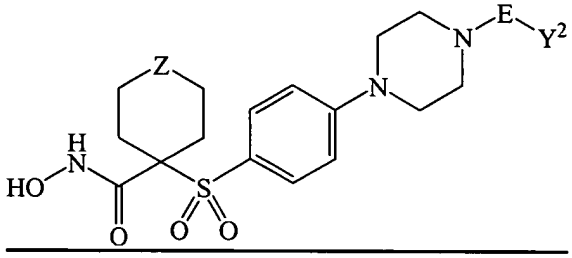
IX



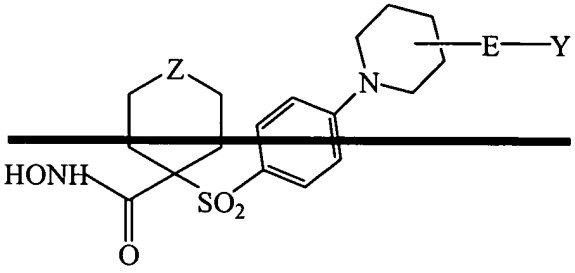
IX-1



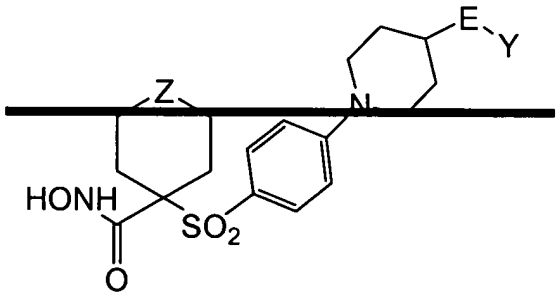
IX-2



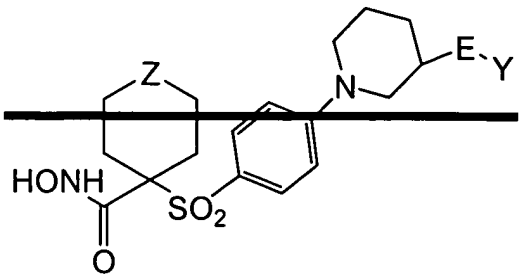
X



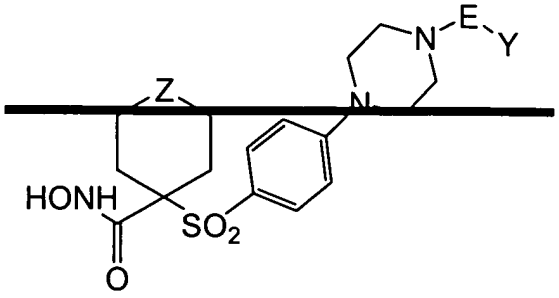
~~**IX**~~



~~**IX-1**~~



~~IX-2~~



~~X~~

The paragraph bridging lines 4-11 on page 32 has been amended in the following manner:

wherein m, n, p, X, Z and Y are as defined above for formula II, g is zero, 1 or 2 and R^{24} is R^3 as defined in formulas I, III or IV, is the substituent G-A-R-E-Y^2 of formula II (formula VIA) or is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

The paragraph bridging line 29 on page 35 to line 9 on page 36 has been amended in the following manner:

In accordance with the present invention, it has been discovered that certain aromatic sulfone hydroxamic acids (**including** hydroxamates) are effective for inhibition of matrix metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ are effective for inhibition of one or more enzymes such as MMP-2, MMP-9 and MMP-13, which can be particularly destructive to tissue if present or generated in abnormal quantities or concentrations, and thus exhibit a pathological activity. Included in that pathological activity is the assistance of tumors and tumor cells in the process of penetrating basement membrane, and developing a new or improved blood supply; i.e., angiogenesis.

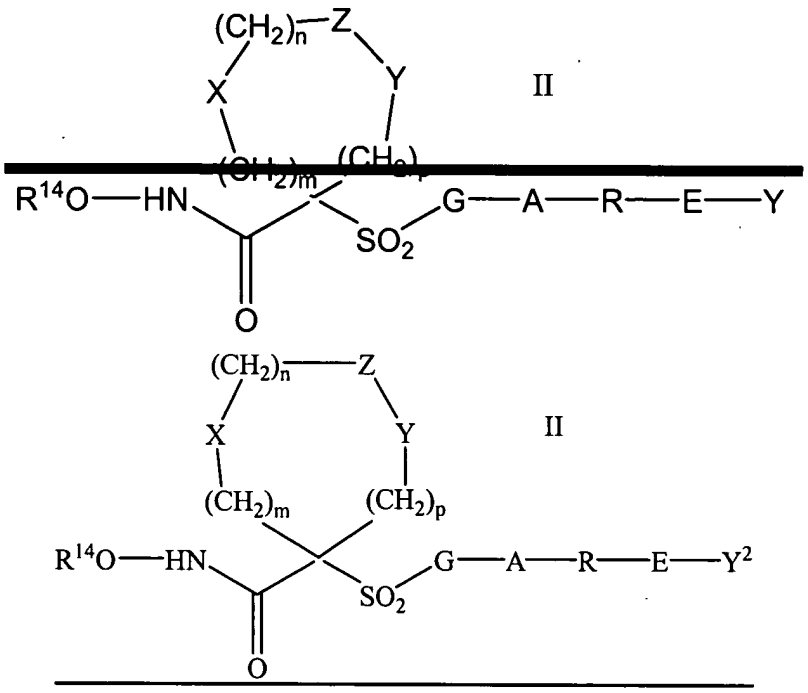
The paragraph bridging lines 10-25 on page 36 has been amended in the following manner:

Moreover, it has been discovered that these aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ are selective in the inhibition of one or more of MMP-2, MMP-9 and MMP-13 without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that a contemplated aromatic sulfone **hydroxamic acid** ~~**hydroxamate**~~ of the invention, or a pharmaceutically acceptable salt thereof, is particularly active in inhibiting of one or more of MMP-2, MMP-9 and MMP-13 in an *in vitro* assay that is predictive of *in vivo* activity. In addition, while being selective for one or more of MMP-2, MMP-9 and MMP-13, a contemplated aromatic sulfone **hydroxamic acid** ~~**hydroxamate**~~, or its salt, has a limited or minimal *in vitro* inhibitory effect on MMP-1.

The paragraph bridging lines 16-31 on page 39 has been amended in the following manner:

Thus, in one embodiment, the present invention is directed to a treatment process that comprises administering a contemplated aromatic sulfone hydroxamic acid metalloprotease inhibitor, or a pharmaceutically acceptable salt thereof, in an effective amount to a host mammal having a condition associated with pathological matrix metalloprotease activity. A contemplated aromatic sulfone **hydroxamic acid** ~~**hydroxamate**~~ inhibitor compound useful in such a process inhibits the activity of one or more of MMP-2, MMP-9 and MMP-13, and exhibits substantially less inhibitory activity against at least MMP-1 in the *in vitro* assay noted above and discussed in detail hereinbelow. An aromatic sulfone **hydroxamic acid** ~~**hydroxamate**~~ inhibitor compound for use in a contemplated process corresponds in structure to formula I, below:

Formula II at line 10 on page 46 has been amended in the following manner:



The paragraph bridging line 27 on page 51 to line 4 on page 52 has been amended in the following manner:

G-A-R-E-Y^{2} is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y^{2} preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

The paragraph bridging lines 24-25 on page 53 has been amended in the following manner:

(9) E is absent and R is bonded directly to Y^{2}; and

The paragraph bridging line 26 on page 53 to line 10 on page 54 has been amended in the following manner:

the moiety Y^{2} is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl,

heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl, aralkyl, or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, trifluoroalkyl, trifluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

The paragraph bridging lines 11-21 on page 54 has been amended in the following manner:

The substituent -G-A-R-E-$Y^{\underline{2}}$ preferably contains two to four carbocyclic or heterocyclic rings, including the aryl or heteroaryl group, G. More preferably, each of those rings is 6-membered. Additional separate preferences for a compound of formula II include: (a) that A is -O- or -S-, (b) R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group, (c) E is absent, and (d) $Y^{\underline{2}}$ is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

The paragraph bridging lines 3-7 on page 62 has been amended in the following manner:

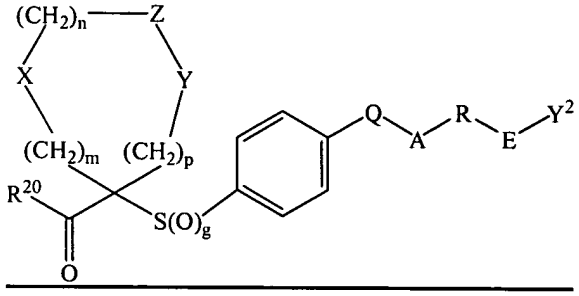
Here, R^3 is as defined above as to formulas I, III and more preferably as defined as to formula II (wherein the R^3 radical is the substituent G-A-R-E-$Y^{\underline{2}}$). Most preferably, R^3 is as defined in formula III.

The paragraph bridging line 20 on page 63 to line 12 on page 64 has been amended in the following manner:

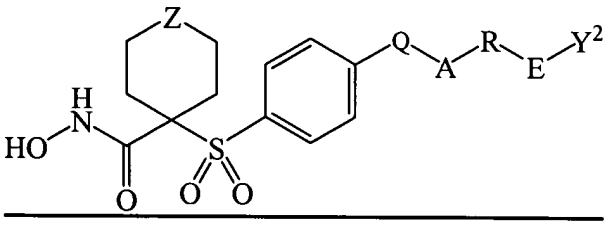
Further compounds of formula A are also particularly preferred. One group of these compounds corresponds in structure to formula B, formula VIC, and more still particularly to formula VIC-1 and formula VIC-2, and formula VIII, below. In those formulas, ring structure Q including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 7-members, preferably 6-members, and can contain zero or one additional nitrogen atom in addition to that depicted. The members of substituent -A-R-E-$Y^{\underline{2}}$ (or -R-E-$Y^{\underline{2}}$ or -E-$Y^{\underline{2}}$) are as defined elsewhere

in the definition of the members of the substituent -G-A-R-E-Y^2. Furthermore, substituent A-R-E-Y^2 (or substituent R-E-Y^2 or E-Y^2) is bonded at the 4-position relative to that depicted nitrogen atom when Q is a 6- or 7-membered ring and at the 3- or 4- position relative to that depicted nitrogen when Q is a 5-membered ring. Still further, R^{20}, X, Y, Z, m, n, and p of the ring system and g are as before described.

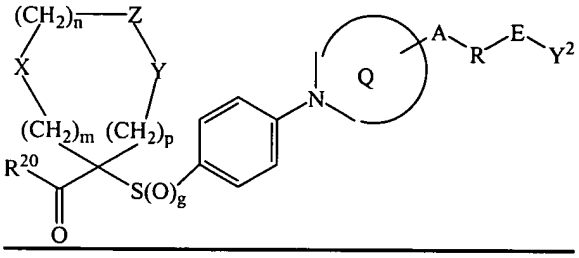
The structures from line 13 on page 64 to line 2 on page 66 have been amended in the following manner:



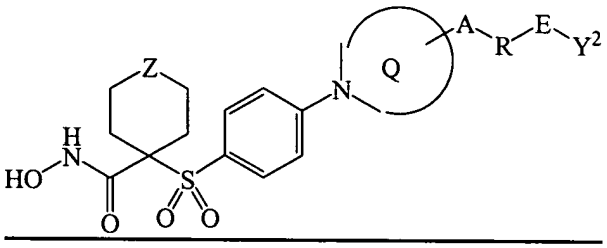
B



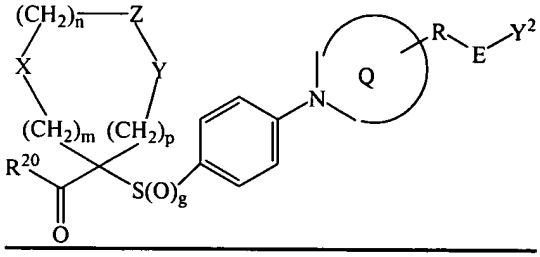
B-A



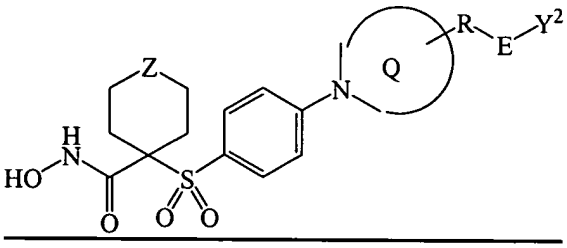
B-1



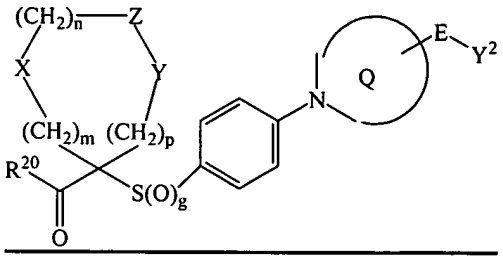
B-1A



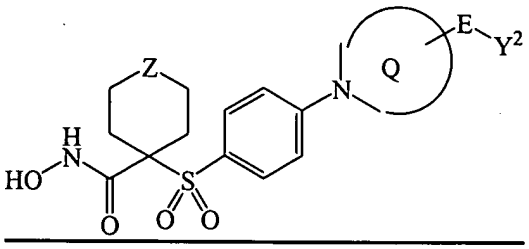
B-2



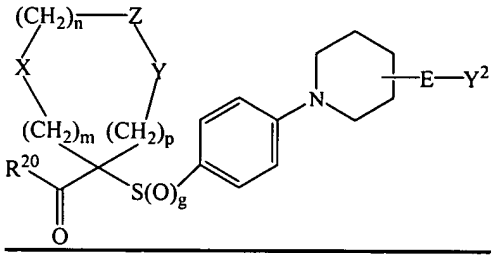
B-2A



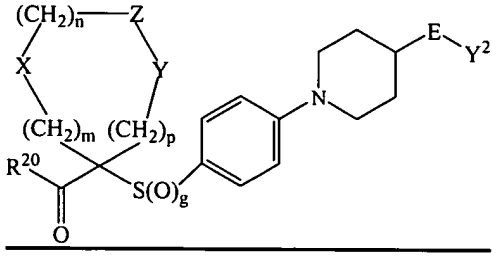
B-3



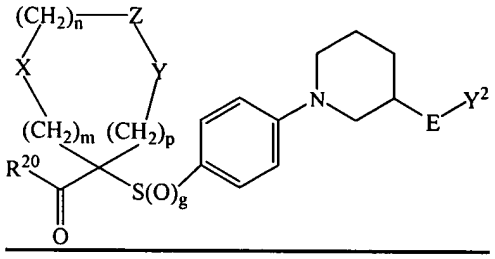
B-3A



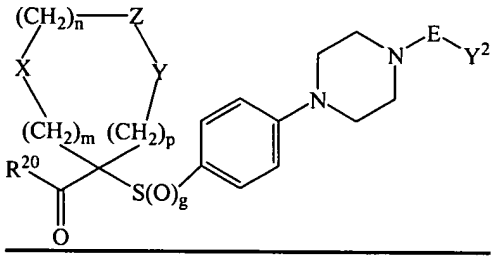
VIC



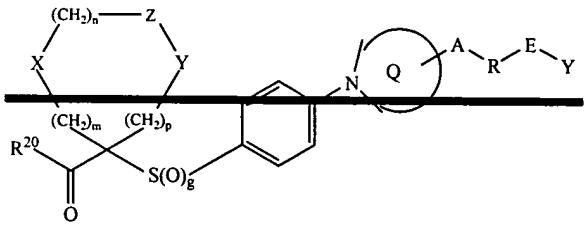
VIC-1



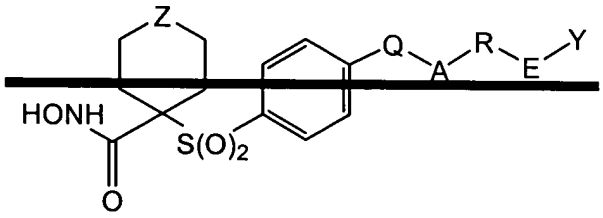
VIC-2



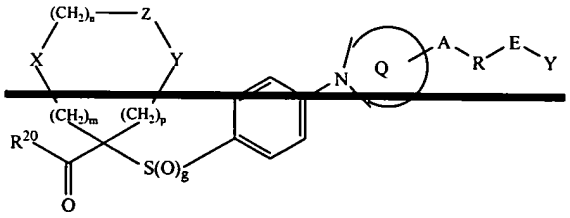
VIII



~~B~~



~~B-A~~



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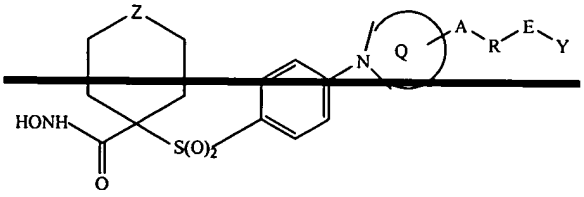

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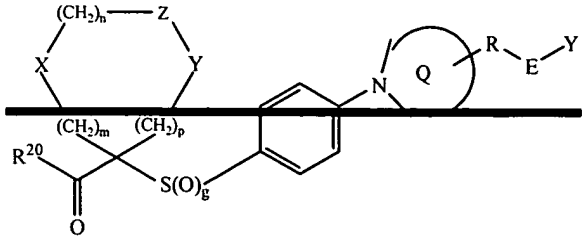

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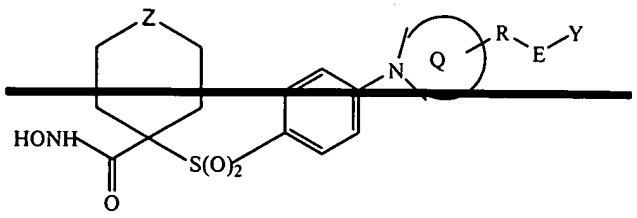
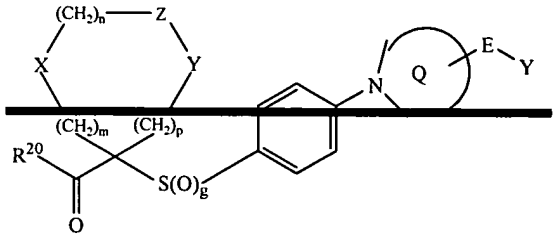


~~B-2A~~



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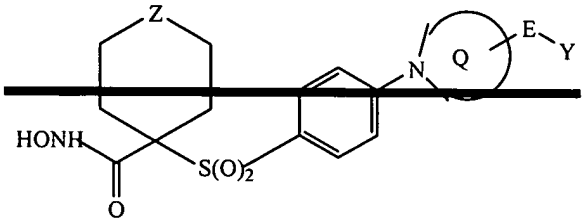
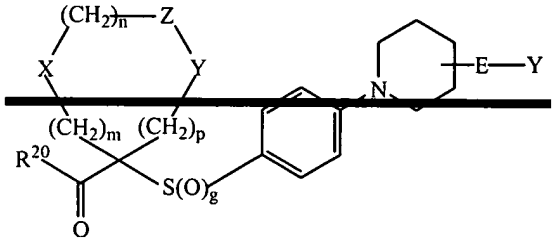
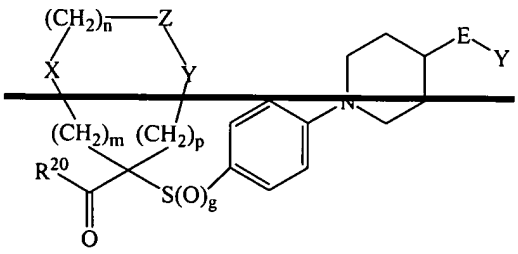


~~B-3A~~



~~VIC~~



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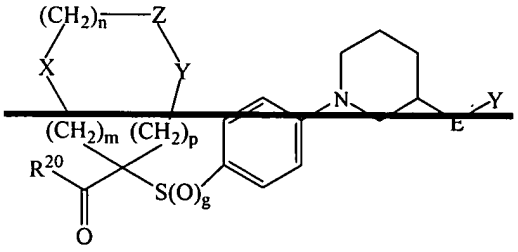

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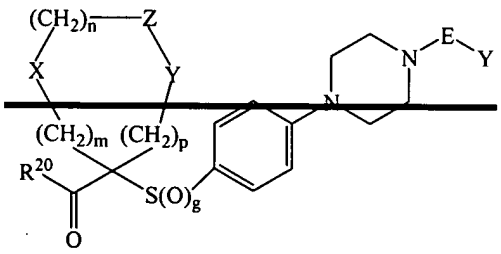
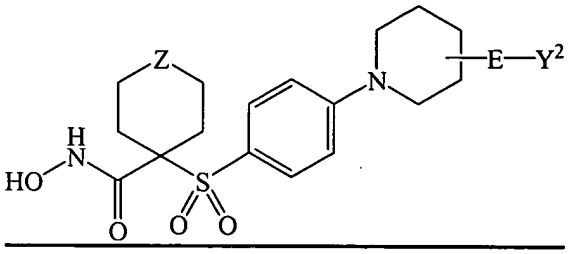


~~VIII~~

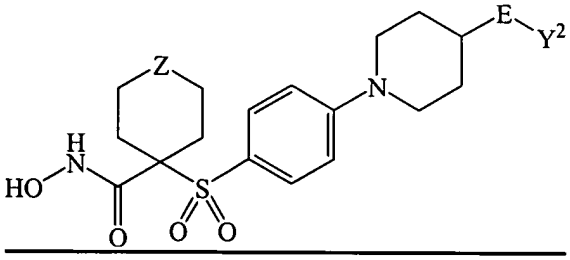
The paragraph bridging lines 3-9 on page 66 has been amended in the following manner:

More particularly preferred among the compounds of formula VIC, formula VIC-1, formula VIC-2, and formula VIII, are the compounds of formulas **B-2,** IX, IX-1, IX-2, X, XI, XI-1, XI-2 and XII, below, wherein Z is as before described and the members of the substituent group -E-Y^2 and -R-E-Y^2 are defined for the substituent group -G-A-R-E-Y^2.

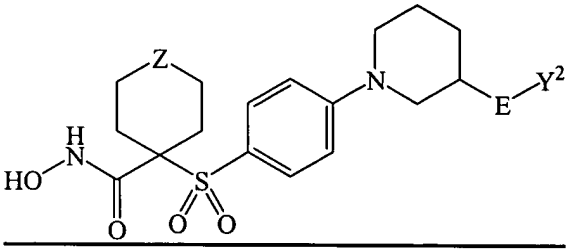
The structures from line 10 on page 66 to line 7 on page 67 have been amended in the following manner:



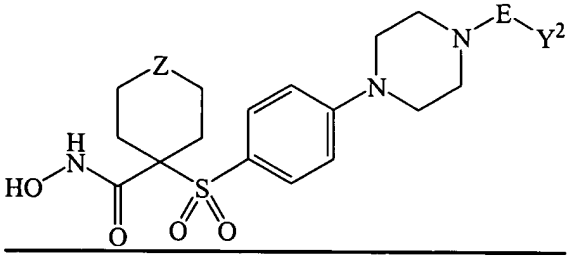
IX



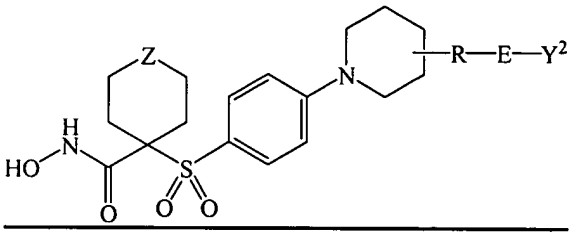
IX-1



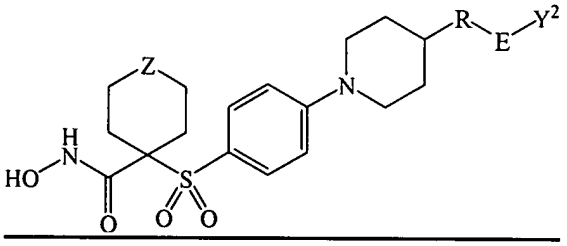
IX-2



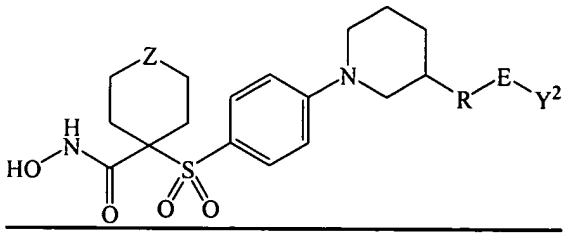
X



XI



XI-1



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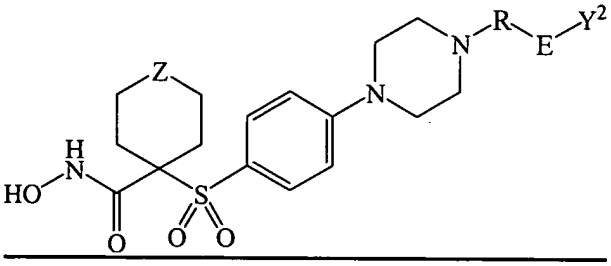

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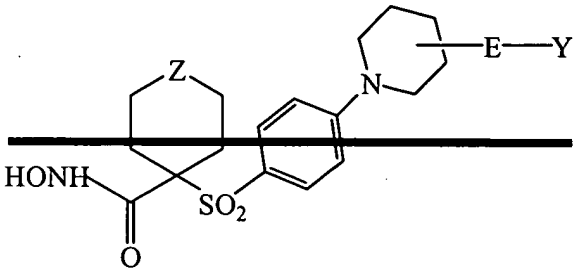
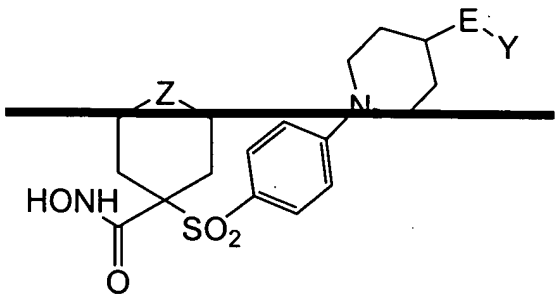


~~IX~~



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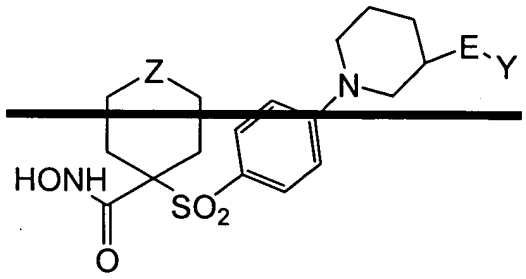
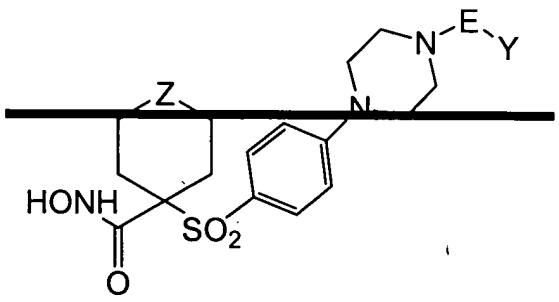
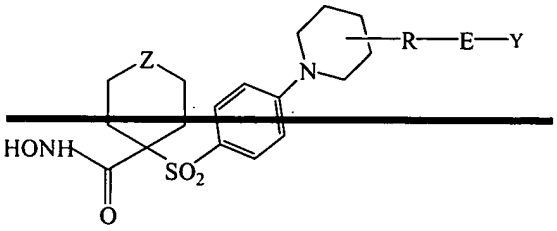


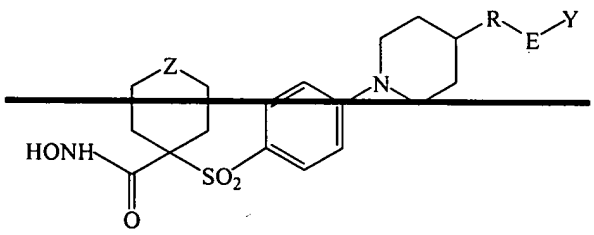
~~IX-2~~



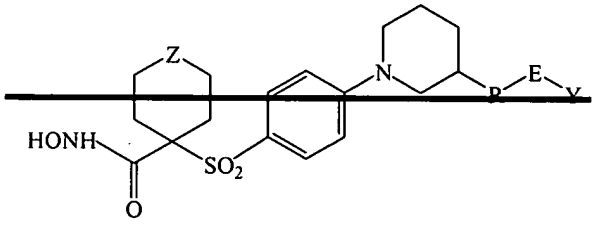
~~X~~



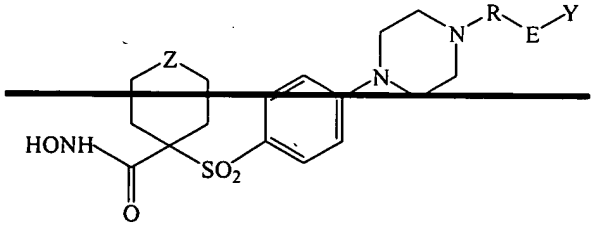
~~XI~~



~~XI-1~~



~~XI-2~~



~~XII~~

The paragraph bridging lines 12-26 on page 75 has been amended in the following manner:

In one embodiment of a particularly preferred aromatic sulfone **hydroxamic acid** ~~hydroxamate~~ inhibitor compound, an R^{23} substituent is phenoxy and is itself substituted at its own para-position with a moiety that is selected from the group consisting of a halogen, a C_1-C_4

alkoxy group, a C_1-C_4 alkyl group, a dimethylamino group, a carboxyl C_1-C_3 alkylene group, a C_1-C_4 alkoxy carbonyl C_1-C_3 alkylene group, a trifluoromethylthio group, a trifluoromethoxy group, a trifluoromethyl group and a carboxamido C_1-C_3 alkylene group, or is substituted at the meta- and para-positions by a methylenedioxy group. It is to be understood that any R^{23} substituent can be substituted with a moiety from the above list. Such substitution at the para-position is preferred.

The paragraph bridging lines 8-14 on page 82 has been amended in the following manner:

R^{24} is R^3 as defined in formulas I, III, IV or is the substituent G-A-R-E-Y^2 of formula II (formula VIA). Alternatively, R^{24} is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

The paragraph bridging line 17 on page 82 to line 10 on page 83 has been amended in the following manner:

Exemplary nucleophilically displaceable leaving groups, D, include a halo (fluoro, chloro, bromo, or iodo) nitro, azido, phenylsulfoxido, aryloxy, C_1-C_6-alkoxy, a C_1-C_6-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar- C_1-C_6-alkyl or C_1-C_6-alkyl. Additional coupling substituents include, without limitation, a hydroxyl group and an amino group that can be coupled with carbonyl-containing moieties to form esters, urethanes, carbonates, amides and ureas. Similarly, a carboxyl coupling substituent can be used to form an ester, thioester or amide. Thus, a coupling substituent is useful in converting a coupling substituent-containing aryl or heteroaryl group into a substituent such as a G-A-R-E-Y^2 substituent discussed hereinabove by the formation of a covalent bond.

The paragraph bridging lines 11-18 on page 83 has been amended in the following manner:

A compound of formula VI can be coupled with another moiety at the $R^{3'}$ coupling substituent to form a compound whose newly formed R^3 group is that of formulas I, III, IV or -G-A-R-E-Y^2. Exemplary of such couplings are the nucleophilic displacement to form ethers and thioethers, as well as the formation of ester, amide, urea, carbonate, urethane and the like linkages.

The paragraph bridging lines 13-22 on page 96 has been amended in the following manner:

The term "aminocarbonyl" (carboxamide) alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amine reacted with a carboxylic acid wherein the amino (amido nitrogen) group is unsubstituted (-NH_2) or a substituted primary or secondary amino group containing one or two substituents selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like, as recited. A **hydroxamic acid** ~~**hydroxamate**~~ is a N-hydroxycarboxamide.

The paragraph bridging line 25 on page 97 to line 15 on page 98 has been amended in the following manner:

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other ~~**physiological**~~ **physiologically** acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated ~~**tertiary**~~ amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid,

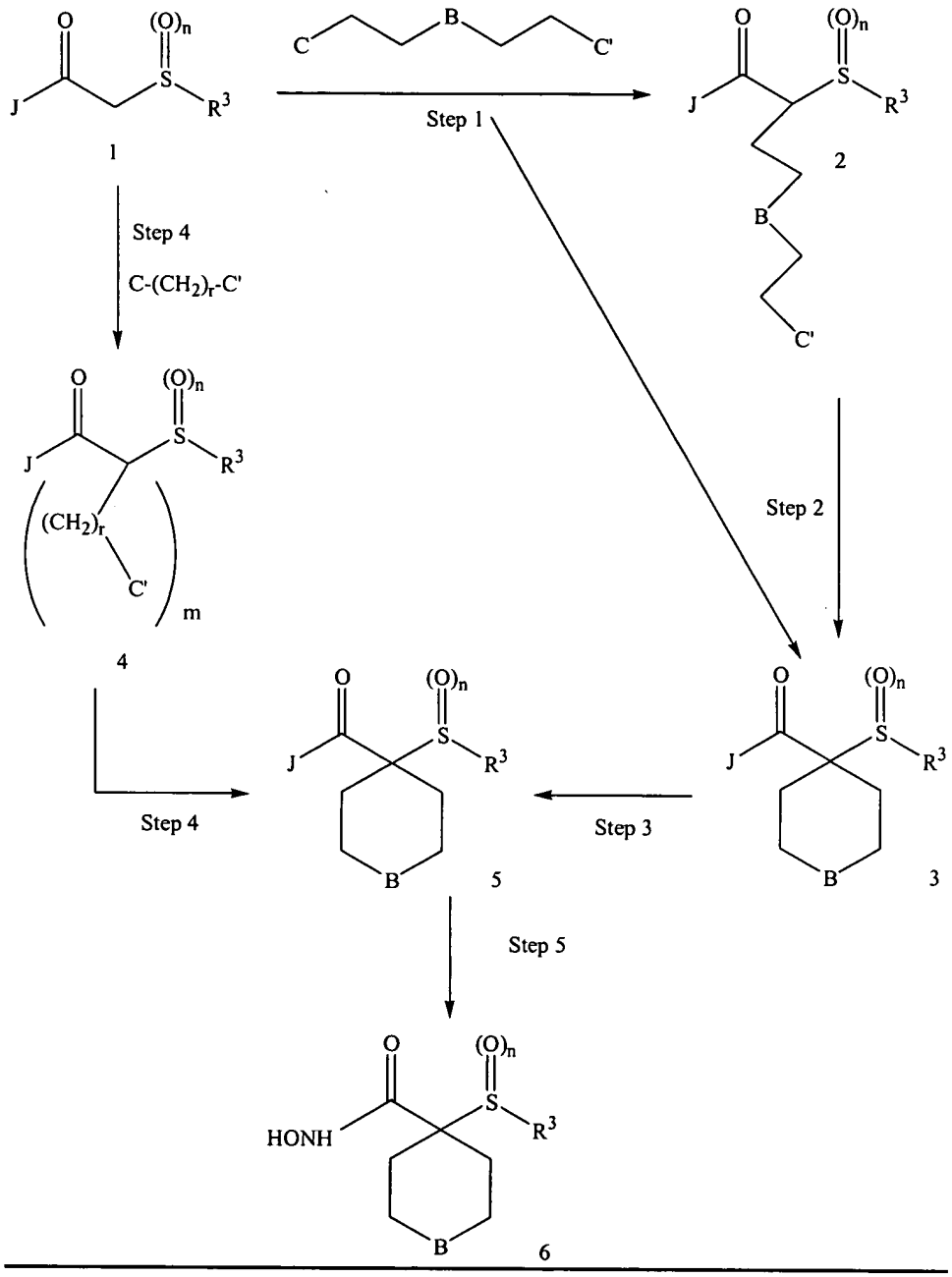
maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

The paragraph bridging lines 23-30 on page 99 has been amended in the following manner:

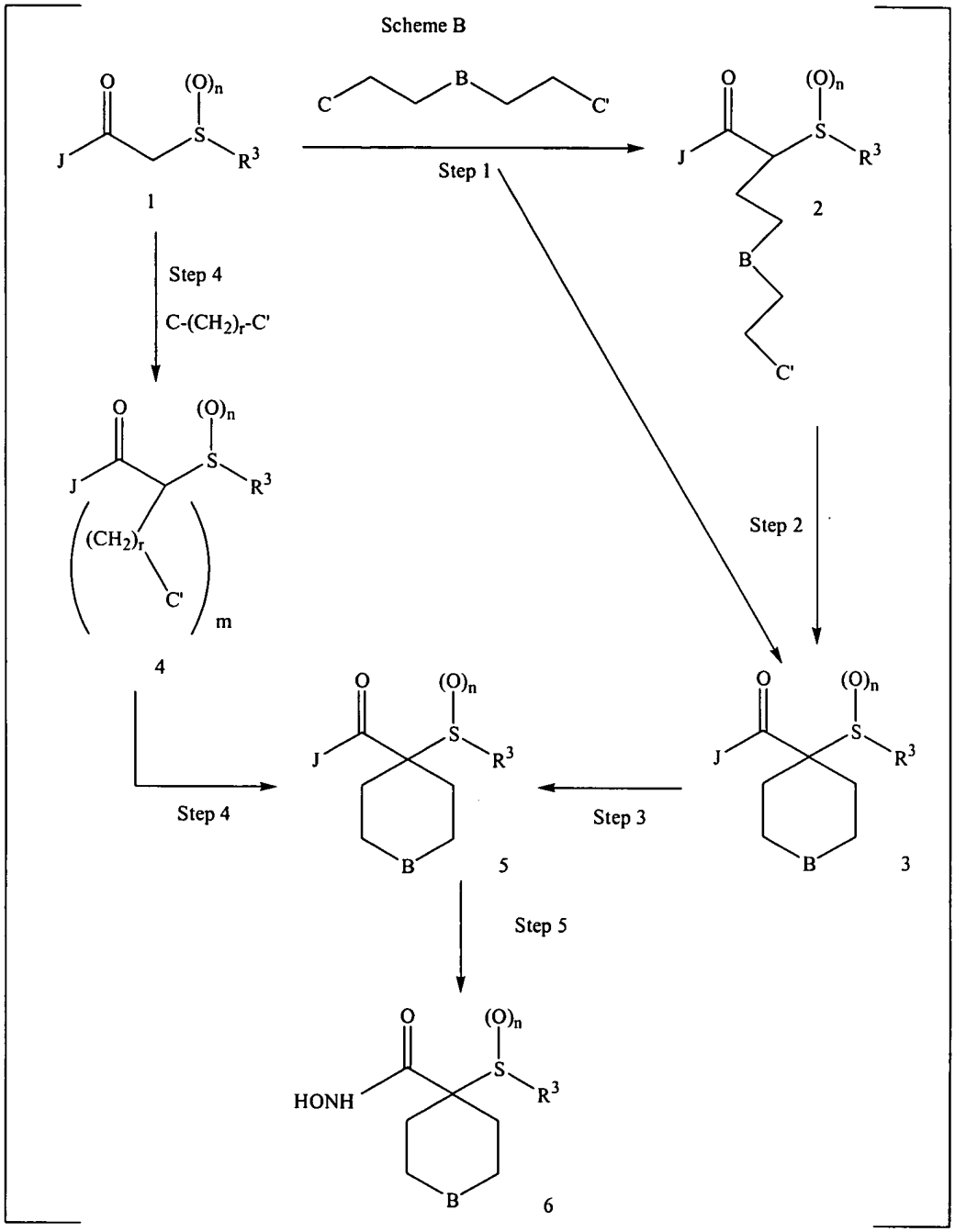
The structures in Schemes 1 through 19 are also shown with compounds that represent the other compounds of this invention. The aromatic ring in Scheme C is aryl and heteroaryl. The moieties of -A-R-E-$Y^{\underline{2}}$ are as defined before. Reactions illustrated involving a spiroheterocyclic nitrogen atom may not be applicable to those compounds with sulfur or oxygen.

Scheme B at line 1 on page 104 has been amended in the following manner:

Scheme B

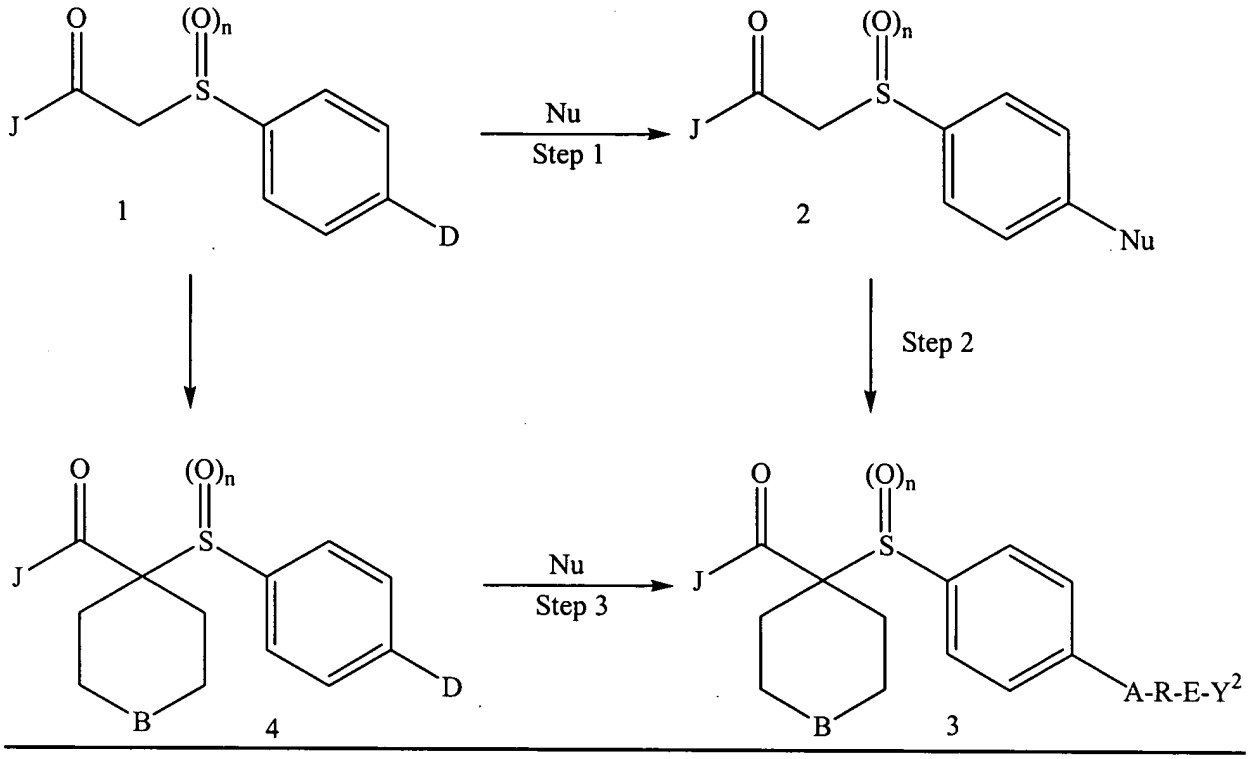


Scheme B

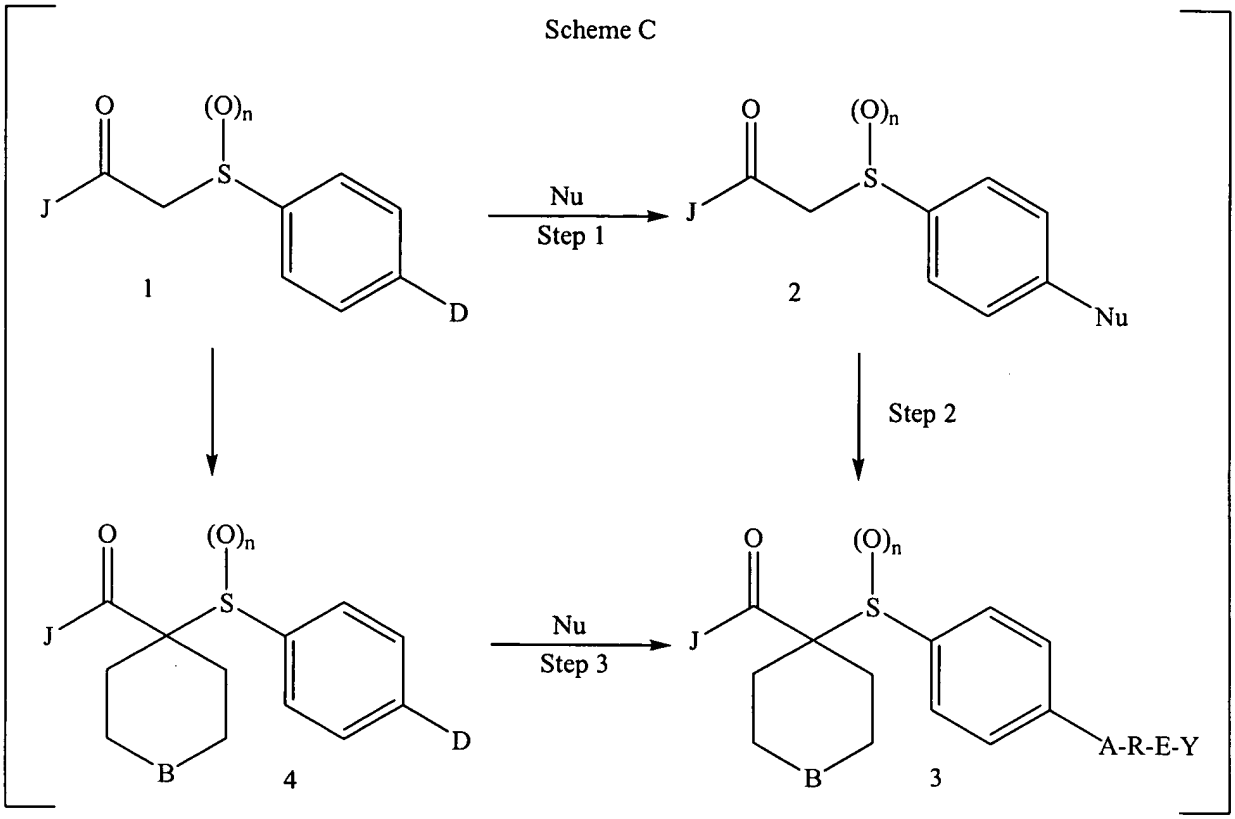


Scheme C at line 17 on page 106 has been amended in the following manner:

Scheme C



Scheme C



The paragraph bridging lines 13-18 on page 107 has been amended in the following manner:

Steps 1, 2 and 3 also illustrate that although the nucleophilic displacement can be carried out with one nucleophile (Nu), the product of this reaction can be modified by methods well known in the art and as shown herein to provide the group -A-R-E-Y^2 as defined hereinbefore.

The paragraph bridging lines 19-31 on page 107 has been amended in the following manner:

A non-limiting illustration of such a process is provided when D is fluoride. The fluoride leaving group can be directly displaced with the anion of 4-trifluoromethylphenol, 4-trifluoromethoxyphenol, 4-trifluoromethylthiophenol and the like to provide a contemplated compound. This is a one pot process from Compound 4. Other compounds included in -A-R-E-Y^2 can be prepared by displacing the fluoride leaving group with ammonia to provide an amine, which can then be acylated by methods discussed wherein with, for example,

4-trifluoromethylbenzoyl chloride, to form another contemplated product compound.

The paragraph bridging line 23 on page 407 to line 2 on page 408 has been amended in the following manner:

Part A: A solution of the hydroxamate of Example 233, part F (50 mg, 0.08 mmol) in water (2 mL) was neutralized with saturated sodium bicarbonate. The aqueous solution was extracted with ethyl acetate. Concentration *in vacuo* provided the **hydroxamic acid** ~~**hydroxamate**~~ free base as an orange solid (35 mg, 75%).

The paragraph bridging line 13 on page 521 to line 3 on page 522 has been amended in the following manner:

More specifically, recombinant human MMP-13, MMP-1, MMP-2 and MMP-9 enzymes were prepared in laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a baculovirus as discussed in V.A. Luckow, Insect Cell Expression Technology, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, **[[67]]** **67(8)**:4566-4579 (1993); O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al., The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992) for further details on use of baculovirus expression systems. The expressed enzyme was purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay.

The paragraph bridging lines 4-28 on page 522 has been amended in the following manner:

MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr. Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the

presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Studies with MMP-7 were carried out at pH 7.5 in the presence of 0.02% 2-mercaptoethanol using conditions otherwise similar to those used for the other enzymes. The enzyme was **obtained** ~~obtaind~~ from a hMMP-7-expressing E. coli clone that was a gift of Dr. Steven Shapiro of Washington University, St. Louis, MO. Further specifics for preparation and use of these enzymes can be found in the scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, Ca (1992) and the citations therein, and **Freije** ~~Frije~~ et al., J. Biol. Chem., **[[26(24)]] 269(24)**: 16766-16773 (1994). The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

The paragraph bridging lines 4-11 on page 549 has been amended in the following manner:

The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, **Kenyon, BM, et al.,** *A Model of Angiogenesis in the Mouse Cornea* ~~; Kenyon,BM, et al.~~, Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8**, pp. 1625-1632**.